JCI The Journal of Clinical Investigation

A STUDY OF MINUTE TO MINUTE CHANGES OF ARTERIO-VENOUS OXYGEN `CONTENT DIFFERENCE, OXYGEN UPTAKE AND CARDIAC OUTPUT AND RATE OF ACHIEVEMENT OF A STEADY STATE DURING EXERCISE IN RHEUMATIC HEART DISEASE

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J Clin Invest. 1954;33(8):1146-1167. https://doi.org/10.1172/JCI102988.

Research Article

A STUDY OF MINUTE TO MINUTE CHANGES OF ARTERIO-VENOUS OXYGEN CONTENT DIFFERENCE, OXYGEN UPTAKE AND CARDIAC OUTPUT AND RATE OF ACHIEVEMENT OF A STEADY STATE DURING EXERCISE IN RHEUMATIC HEART DISEASE

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(Submitted for publication January 21, 1954; accepted April 22, 1954)

When the Fick equation for the estimation of the cardiac output is applied to the values obtained from a few mixed venous blood samples drawn during a period of measurement of oxygen uptake, they should be truly representative of the values throughout that period. This is most unlikely to be the case unless the subject is in a steady state. The Fick principle with cardiac catheterization has frequently been employed to measure the cardiac output of patients with rheumatic heart disease during exercise, the measurements being made after an arbitrary period varying from two to ten minutes, after which it has been hoped, but never proved, that a steady state had been reached, even in patients with gross disability. Cournand (1), who has at all times emphasized these difficulties, considers the steadiness of the oxygen consumption, of the respiratory quotient and of the pulse rate useful criteria of constant levels of blood oxygenation and cardiac output.

In the work reported here the standard Fick method has been modified and mixed venous and arterial blood samples have been collected frequently throughout a period of exercise and recovery in a number of patients with rheumatic heart disease, mainly involving the mitral valve. The percentage saturation of the mixed venous blood entering the lungs can be closely followed by the technique described even in a rapidly changing state. However, if the mean (in time) A–V difference [1] is employed in the Fick formula to calculate the cardiac output while both the A–V difference and blood flow are changing then some error will ensue. The magnitude and importance of such errors will be discussed later in relation to the results. Particular attention has been paid to the rate of achievement of a steady hemodynamic state during exercise. A similar series of studies has been carried out on normal subjects, which although briefly mentioned for comparative purposes, is being reported fully elsewhere (2).

[1] Throughout this article "A–V difference" is used to denote the arterio-venous oxygen content difference.

SUBJECTS, METHODS AND PROCEDURE

The sixteen subjects studied had been presented for consideration of mitral valvulotomy. Ten of these patients had mitral stenosis (M.S.), two mitral stenosis and mitral regurgitation (M.S. & R.), two predominant mitral regurgitation (M.R.), and two mitral and aortic stenosis (M. & A.S.) None had evidence of active rheumatism or of congestive failure. All were taking digitalis with the exception of cases C1, C7, and C10. Clinical data concerning each patient is given in the Appendix. There were a number of important modifications of the standard methods.

Blood oxygenation and arterio-venous oxygen content difference

The almost continuous observation of the arterio-venous oxygen content difference by the sampling of arterial and mixed venous blood at frequent intervals necessitated the rapid and accurate analysis of very large numbers of blood samples and a spectrophotometric method was therefore developed. Briefly, 2 ml. samples of blood were anaerobically diluted (about 1 in 5) with a hemolyzing solution and an aliquot of this solution placed in sample tubes made from ordinary glass tubing, the remainder being set aside for oxygenation. These tubes were marked and the same light path employed throughout. The optical density of the tube and solution was then determined using a standard Unicam spectrophotometer. The optical density was again determined after complete reduction of the hemoglobin by a drop of saturated sodium hydrosulphite solution. The tube was then cleaned and filled with the oxygenated solution, and the optical density determined once more. The percentage saturation was then easily calculated. The oxygen capacity of the blood sampled at rest and during exercise was measured by the Van Slyke manometric or standard photometric methods and thus the oxygen content of the blood samples determined. A duplicate estimation of percentage saturation was carried out on all blood samples. The technique and accuracy, which is most satisfactory as

compared with standard Van Slyke estimations, has been reported elsewhere (3). The small size of the individual blood samples allowed frequent sampling without undue blood loss.

Ventilation and oxygen uptake

During exercise and recovery the expired air was collected in a Tissot spirometer. A tracing was taken which was interrupted by a minute signal and during each minute the expired air was sampled at a constant rate by mercury siphoning from a side arm near the spirometer and separated from the mouthpiece by 3 feet of corrugated tubing. Haldane gas sampling tubes of 50 ml. capacity were employed and only a few seconds at the end and beginning of each minute were needed to change the gas sampling tubes. Gas samples were analysed for oxygen and carbon dioxide content by the Scholander micromethod and duplicate analyses were required to check by 0.03 per cent. It was appreciated that simultaneous changes in ventilation and oxygen extraction would cause some error in the determination of oxygen uptake by this method and this is discussed further in the section dealing with sampling errors. A series of experiments was carried out on patients with comparable cardiac disability in which the oxygen uptake over a minute was measured simultaneously by both side-arm sampling and by the standard technique of sampling from the Tissot spirometer. These results were compared in 21 instances, measurements being made during a steady state of exercise, in the first minute of exercise and in the first minute of recovery. The results obtained are shown in Figure 1.

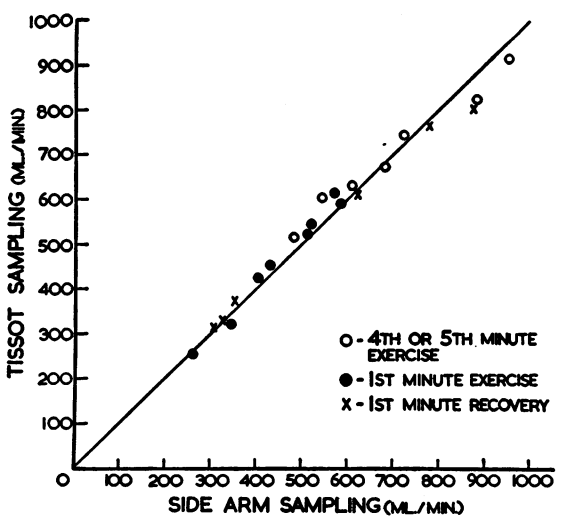

FIG. 1. COMPARISON OF SIMULTANEOUS OXYGEN UPTAKE MEASUREMENTS (N.T.P.), BY CONTINUOUS SIDE ARM AND BY SPIROMETER SAMPLING, DURING EXERCISE AND RECOVERY, IN PATIENTS WITH HEART DISEASE

The coefficient of correlation between the two series of measurements is $r = 0.99$ $(n = 21)$ and the standard difference within pairs of measurements is 21.8 ml.

Although the error is small and non-systematic, if the authors were repeating this type of study they would favour the use of a number of 50 liters-capacity, light rubberized gaberdine "Douglas" bags so that each minute's expirate could be collected separately and measured and analysed after the experiment.

Exercise

Great care was taken to ensure a constant level of work. The subjects exercised in the horizontal position on a bicycle ergometer fixed to the foot of the screening table. The shoulders were steadied by supports so that the subject was able to bear easily and comfortably on the pedals. Above the apparatus was a simple differential indicator, one side being geared to the flywheel and the other to a gramophone motor with the governor lever in a fixed position. The patient and all members of the team could watch the movements of the differential arm and thus ensure a steady rate of pedalling. The degree of work was varied from subject to subject by altering the tension of the friction belt on the flywheel. All subjects were shown the apparatus the day before the study, and, with little practice, were able to pedal at a steady rate. In each case the maximum degree of work which could be sustained for five minutes without undue distress was chosen. Thus all the studies were at levels of exercise close to the tolerance of the patient.

Pressure recording

Vascular pressures were recorded by means of capacitance manometers. The degree of damping and conditions of adequate manometric performance were as previously described (4). The manometric zero was fixed 10 cm. above the table on which the patient was lying. The zero setting and calibration of the electromanometer were checked frequently, particularly before and after any important pressure measurements.

Procedure

Each subject was given 0.4 Gm. of quinidine sulphate by mouth three hours before the procedure; 0.13 to 0.2 Gm. of sodium amytal were also given two and one hours previously. No meal had been taken for six hours but 50 Gm. of glucose in a fruit drink were given half an hour before the catheterization. The resting cardiac output was determined and pressure measurements made fifteen minutes after the tip of the catheter had been passed into the pulmonary artery and an indwelling arterial needle inserted into the brachial artery, providing the patient was settled and the minute ventilation steady. During the three-minute period of expired air collection, three 3 ml. samples of mixed venous and arterial blood were taken.

Thirty seconds before the commencement of exercise a sample of mixed venous blood was taken. Fifteen seconds before, the legs were raised and the feet steadied on the pedals. Five seconds before, the pedals were started by team members to overcome the initial inertia and to achieve rapidly the required rate of pedalling.

TABLE I

Observations at rest and during five minutes exercise and recovery

Subject	Minute of study*	O_2 Consum. (*ml./min./m.²*) N.T.P.	A-V diff. (*vols. %*) N.T.P.	C.I. (*L./min./m.²*)	Heart rate	Stroke vol. (*ml.*)	Vent. (*L./min./m.²*) N.T.P.	R.Q.	% O_2 extn.	Pressure (*mm. Hg*) Mean P.A.	B.A. (S)	B.A. (D)
C1	Rest	160	3.78	4.21	90	79	3.33	.79	4.78	20	110	78
	Ex. 1	330	5.63	5.85	112	88	6.68	.85	4.93	—	—	—
SA = 1.68 m.²	2	524	8.88	5.90	124	80	8.64	.75	6.06	—	—	—
RC = 21.10†	3	602	8.88	6.79	129	88	9.30	.77	6.48	—	—	—
EC = 21.65	4	564	8.88	6.36	135	79	9.30	.85	6.07	—	—	—
	5	548	8.88	6.17	134	77	9.13	.84	6.00	30	—	—
	Ry. 2	220	5.85	3.75	—	—	5.87	1.08	3.74	—	—	—
	5	142	3.25	4.35	—	—	4.08	1.04	3.47	17	—	—
C2	Rest	176	5.11	3.44	84	66	5.62	1.06	3.12	29	112	64
	Ex. 1	332	5.85	5.67	104	87	7.91	.92	4.20	—	160	90
SA = 1.60 m.²	2	511	9.83	5.19	122	68	10.54	.83	4.93	—	160	90
RC = 16.70	3	696	10.19	6.83	135	81	14.06	.93	4.95	—	160	88
EC = 18.20	4	710	10.10	7.03	140	80	14.76	.97	4.81	66	152	82
	5	742	9.28	7.99	136	94	15.81	1.02	4.69	50	144	84
	Ry. 2	373	5.92	6.79	114	88	12.92	1.36	2.84	—	130	78
	5	191	5.82	3.29	111	47	7.32	1.22	2.59	35	100	68
C3	Rest	108	5.10	2.12	66	51	3.32	.84	3.26	38	140	70
	Ex. 1	209	9.17	2.28	106	34	6.43	.88	3.24	—	140	94
SA = 1.60 m.²	2	516	14.43	3.58	138	41	12.25	.83	4.21	—	140	96
RC = 18.80	3	493	15.99	3.08	153	32	16.31	1.09	3.02	—	148	96
EC = 19.50	4	628	15.31	4.10	153	43	18.69	1.07	3.36	65	140	80
	5	538	15.41	3.49	—	—	16.75	1.07	3.21	—	—	—
	Ry. 1	379	12.09	3.13	78	64	10.31	1.04	3.67	54	155	80
	2	214	6.92	3.09	79	63	8.03	1.38	2.67	—	—	—
	3	167	6.24	2.68	82	52	6.35	1.34	2.63	—	130	70
	4	151	5.66	2.67	87	49	5.59	1.28	2.69	—	120	65
	5	147	4.97	2.95	84	56	5.50	1.18	2.67	45	125	70
C4	Rest	134	4.49	2.99	67	66	4.06	.89	3.30	35	104	56
	Ex. 1	298	6.39	4.66	102	68	10.09	1.07	2.95	—	—	—
SA = 1.49 m.²	2	476	10.12	4.70	132	53	12.56	.84	3.79	—	124	68
RC = 18.25	3	596	10.65	5.60	146	57	18.28	1.00	3.26	—	144	72
EC = 17.75	4	552	10.56	5.22	149	52	20.00	1.08	2.76	65	144	72
	5	516	10.83	4.77	—	—	20.00	1.14	2.58	—	—	—
	Ry. 2	232	5.95	3.91	90	65	9.71	1.25	2.39	40	—	—
	5	149	4.79	3.11	80	58	5.23	.99	2.84	35	—	—
C5	Rest	163	5.59	2.93	87	54	4.53	.93	3.61	40	100	62
	Ex. 1	284	8.72	3.27	129	41	7.53	.91	3.78	—	120	80
SA = 1.61 m.²	2	498	13.24	3.76	158	38	13.14	.94	3.79	—	120	80
RC = 20.11	3	606	14.35	4.22	168	41	16.83	1.18	3.60	—	120	80
EC = 21.26	4	642	15.03	4.27	178	37	19.20	1.26	3.35	55	120	80
	5	663	16.05	4.13	175	38	20.85	1.26	3.18	—	120	80
	Ry. 1	564	13.54	4.17	163	41	15.67	1.21	3.60	—	95	70
	2	333	8.61	3.87	143	44	14.55	1.71	2.29	60	110	70
	3	237	7.29	3.25	110	48	12.09	1.67	1.96	—	100	65
	4	204	6.80	3.00	85	57	10.68	1.54	1.91	—	100	60
	5	197	6.59	2.99	80	60	9.29	1.39	2.12	45	100	60
C6	Rest	136	5.22	2.59	72	55	3.80	.92	3.56	32	110	60
	Ex. 1	180	6.51	2.77	104	41	5.60	.86	3.22	—	130	70
SA = 1.52 m.²	2	439	11.58	3.80	120	48	9.75	.85	4.51	—	135	75
RC = 19.86	3	447	12.57	3.56	135	40	10.47	.90	4.27	—	120	70
EC = 20.61	4	450	13.29	3.39	135	38	11.30	.96	3.98	66	120	75
	5	445	13.60	3.28	—	—	12.23	1.05	3.64	—	—	—
	Ry. 1	415	12.12	3.43	88	59	13.90	1.09	2.99	—	140	65
	2	226	7.38	3.05	85	55	10.78	1.46	2.09	45	100	60
	3	159	6.18	2.57	85	46	7.47	1.32	2.13	—	96	58
	4	137	6.02	2.28	88	39	6.22	1.24	2.20	—	90	56
	5	147	6.25	2.36	88	41	5.90	1.11	2.49	38	98	60

* Ex = Exercise, Ry = Recovery.

† RC and EC = Resting and Exercising blood oxygen capacity (vols. %).

TABLE I—*Continued*

Subject	Minute of study*	O_2 Consum. (*ml./min./m.²*) N.T.P.	A-V diff. (*vols. %*) N.T.P.	C.I. (*L./min./m.²*)	Heart rate	Stroke vol. (*ml.*)	Vent. (*L./min./m.²*) N.T.P.	R.Q.	% O_2 extn.	Pressure (*mm. Hg*) Mean P.A.	B.A. (S)	B.A. (D)
C7	Rest	141	3.92	3.61	95	60	6.02	.94	2.35	65	100	60
	Ex. 1	209	5.28	4.16	118	56	9.66	.90	2.17	—	110	66
SA = 1.58 m.²	2	301	8.06	3.74	133	44	14.63	.90	2.06	—	115	70
RC = 19.24	3	347	9.22	3.77	140	43	18.97	1.01	1.83	—	112	70
EC = 19.39	4	377	9.35	4.08	146	44	20.68	1.07	1.82	85	112	70
	5	411	9.50	4.33	147	47	22.84	1.09	1.80	—	114	72
	Ry. 1	375	8.64	4.34	143	48	19.05	1.05	1.97	—	110	70
	2	238	5.53	4.30	129	53	13.46	1.02	1.77	73	108	60
	5	151	3.99	3.77	99	60	7.87	.98	1.91	62	106	60
C8	Rest	140	4.96	2.83	72	64	4.26	.90	3.30	48	100	60
	Ex. 1	240	7.60	3.15	94	55	6.73	.84	3.56	—	120	75
SA = 1.64 m.²	2	317	10.78	2.94	113	43	8.11	.79	3.91	—	120	75
RC = 19.30	3	361	11.86	3.04	120	42	10.15	.85	3.56	—	—	—
EC = 19.60	4	334	12.56	2.66	120	36	9.84	.87	3.39	25‡	124	72
	5	358	12.94	2.77	125	36	10.53	.92	3.40	—	120	68
	Ry. 2	201	5.62	3.59	92	64	5.96	.97	3.38	18‡	106	62
	3	164	3.47	4.72	89	87	5.27	1.04	3.11	—	100	60
	4	142	3.33	4.27	85	82	4.86	1.03	2.94	—	100	60
	5	131	3.72	3.53	84	69	4.49	1.01	2.92	18‡	102	62
C9	Rest	146	4.82	3.12	82	53	4.74	.98	3.06	52	100	60
	Ex. 1	253	7.59	3.33	123	39	9.51	1.04	2.66	—	130	70
SA = 1.45 m.²	2	357	12.10	2.95	153	28	13.35	.98	2.67	—	130	70
RC = 18.84	3	397	13.08	3.18	165	28	17.54	1.10	2.37	—	130	70
EC = 20.24	4	474	14.21	3.33	168	29	19.84	1.10	2.39	83	130	70
	5	494	14.97	3.30	163	29	21.14	1.16	2.34	—	120	70
	Ry. 1	394	12.87	3.06	155	29	15.86	1.14	2.49	—	110	58
	2	234	8.34	2.95	130	33	11.96	1.27	2.05	80	120	70
	3	215	7.16	3.01	108	40	9.08	1.18	2.37	—	106	66
	4	199	6.44	3.08	103	43	7.68	1.07	2.59	—	—	—
	5	183	6.11	3.00	100	44	6.78	1.04	2.71	76	100	62
C10	Rest	184	4.76	3.86	108	57	6.25	.93	2.94	65	110	62
	Ex. 1	328	6.72	4.89	122	64	14.20	1.09	2.31	—	104	56
SA = 1.59 m.²	2	355	8.80	4.04	138	47	20.54	1.33	1.73	—	100	52
RC = 11.05	3	430	9.29	4.62	148	50	24.53	1.43	1.75	—	88	56
EC = 12.05	4	418	9.74	4.29	150	46	25.62	1.49	1.63	78	86	52
	Ry. 1	382	10.28	3.71	148	40	22.45	1.44	1.70	80	104	52
	2	360	8.86	4.07	143	45	20.37	1.44	1.77	—	132	68
	3	297	6.51	4.56	133	55	17.47	1.42	1.70	80	146	72
	4	270	5.25	5.16	123	67	15.20	1.38	1.78	—	146	72
	5	208	4.70	4.43	115	61	12.30	1.34	1.69	—	140	72
	6	177	5.30	3.33	110	48	10.32	1.26	1.71	78	140	70
C11	Rest	149	5.26	2.84	115	36	5.05	.89	2.96	50	100	60
	Ex. 1	227	7.47	3.05	138	32	8.09	.88	2.81	—	110	76
SA = 1.46 m.²	2	318	9.64	3.06	160	28	10.31	.83	3.08	—	110	76
RC = 18.00	3	335	10.77	3.11	168	27	12.23	.96	2.74	—	110	76
EC = 18.90	4	345	11.15	3.10	158	29	13.28	1.04	2.60	75	114	78
	5	366	11.06	3.32	153	32	13.67	1.03	2.68	—	—	—
	Ry. 1	301	9.64	3.12	148	31	10.50	1.00	2.87	69	—	—
	2	190	6.71	2.84	139	30	8.18	1.09	2.33	60	102	76
	3	163	5.67	2.88	129	33	6.90	1.09	2.36	—	100	80
	4	142	6.24	2.27	110	30	6.68	1.09	2.12	—	—	—
	5	147	5.95	2.47	102	35	6.16	1.05	2.39	56	102	76
C12§	Rest	162	6.20	2.61	115	39	5.24	.97	3.09	65	130	80
	Ex. 1	230	8.17	2.82	140	34	7.78	.94	2.96	72	—	—
SA = 1.70 m.²	2	312	10.25	3.05	148	35	9.35	.90	3.34	—	—	—
RC = 18.35	3	349	11.28	3.09	150	35	12.25	.94	2.85	80	—	—
EC = 19.45	4	344	11.86	2.90	155	32	13.23	1.01	2.60	—	130	80
	5	364	12.06	3.01	155	33	13.41	1.00	2.71	—	—	—
	Ry. 2	241	9.82	2.46	100	42	8.94	1.01	2.70	70	—	—
	5	196	7.97	2.46	110	38	6.62	.94	2.96	65	—	—

‡ Atrial pressures.
§ Atrial sampling throughout; PA pressures recorded during comparable study.

TABLE I—*Continued*

Subject	Minute of study*	O_2 Consum. (*ml./min./m.²*) N.T.P.	A-V diff. (*vols. %*) N.T.P.	C.I. (*L./min./m.²*)	Heart rate	Stroke vol. (*ml.*)	Vent. (*L./min./m.²*) N.T.P.	R.Q.	% O_2 extn.	Pressure (*mm. Hg*) Mean P.A.	B.A. (S)	B.A. (D)
C13	Rest	137	5.93	2.31	80	55	4.43	.89	3.09	55	118	76
	Ex. 1	188	6.82	2.76	91	58	6.41	.90	2.94	—	150	95
SA = 1.90 m.²	2	214	9.87	2.16	94	44	8.51	.88	2.51	—	160	96
RC = 17.50	3	254	11.31	2.24	91	47	9.34	.92	2.71	—	150	92
EC = 17.95	4	261	11.67	2.24	100	43	9.64	.94	2.71	78	144	92
	5	243	11.49	2.12	115	35	9.34	.98	2.51	78	144	90
	Ry. 2	163	8.26	1.97	80	47	6.25	.98	2.60	68	120	74
	5	129	6.82	1.89	74	49	4.82	.97	2.67	60	120	88
C14	Rest	128	5.01	2.56	80	53	3.69	.94	3.48	40	124	76
	Ex. 1	147	7.47	1.97	101	32	3.49	.88	4.22	60	140	90
SA = 1.65 m.²	2	263	9.50	2.77	110	42	6.02	.81	4.37	70	140	90
RC = 19.60	3	273	10.50	2.60	105	41	6.54	.85	4.17	70	140	90
EC = 20.20	4	261	11.10	2.35	110	35	6.80	.90	3.84	82	140	90
	5	263	11.71	2.25‖	133	28	7.22	—	—	75	—	—
	Ry. 3	205	6.87	2.99	90	55	5.76	.98	3.57	55	—	—
	5	131	6.67	1.96	90	36	3.49	.92	3.75	45	—	—
C15	Rest	176	7.14	2.47	97	42	4.89	.91	3.60	68	104	72
	Ex. 1	216	9.11	2.37	128	30	6.31	.90	3.42	—	108	74
SA = 1.64 m.²	2	273	11.63	2.34	148	26	9.00	.97	3.03	—	120	78
RC = 18.64	3	299	12.17	2.46	160	25	10.37	1.03	2.88	—	120	80
EC = 19.14	4	273	12.00	2.27	168	22	10.71	1.14	2.55	85	120	80
	5	268	12.38	2.16	160	22	11.23	1.15	2.39	—	124	80
	Ry. 1	227	12.13	1.88	152	20	8.81	1.12	2.58	—	122	80
	2	201	9.41	2.13	141	25	7.60	1.14	2.64	—	124	80
	3	182	8.07	2.26	111	33	6.62	1.11	2.75	—	124	76
	4	173	7.73	2.24	121	30	6.13	1.09	2.82	—	124	76
	5	179	8.29	2.16	147	24	5.70	.93	3.14	70	118	82
C16	Rest	135	9.68	1.39	68	36	4.30	.96	3.13	55	120	70
	Ex. 1	157	10.25	1.53	117	23	6.07	1.00	2.58	—	120	70
SA = 1.76 m.²	2	184	13.55	1.35	140	17	7.69	.94	2.39	—	120	70
RC = 20.34	3	232	15.96	1.45	140	18	9.57	.99	2.43	—	130	70
EC = 20.90	4	245	17.43	1.40	140	18	11.28	1.09	2.17	64	120	70
	5	299	17.96	1.66	140	21	12.14	1.08	2.46	—	120	70
	Ry. 1	295	17.22	1.71	123	24	10.97	1.06	2.69	—	115	70
	2	235	15.92	1.48	103	25	10.08	1.13	2.33	—	120	70
	5	151	12.39	1.22	90	24	6.30	1.10	2.40	30‡	130	70

‖ O_2 extraction assumed from mean of mins. 2, 3, and 4.

Exercise continued for five minutes at a steady rate. During this period, and for five minutes thereafter, two to four 3 ml. samples of mixed venous blood were drawn through the catheter each minute, the greater number of samples being taken during early exercise and early recovery. In the short intervals between sampling, the collecting arm of the manifold was allowed to drip slowly to ensure that the initial blood drawn from the catheter was representative of the inflowing mixed venous blood. Arterial blood samples were taken every one or two minutes, but if arterial blood desaturation was suspected, sampling was more frequent. All blood samples were drawn at as steady a rate as possible and the times of each sampling period noted. Meanwhile the expired air was collected in the Tissot spirometer and expired gas sampled throughout each minute. If the spirometer bell became nearly full during the study, the expired air was diverted to a Douglas bag while the bell was emptied.

Pulmonary artery pressures were recorded at rest and as often during exercise and recovery as was feasible. This could be done rapidly by turning the manifold connection attached to the catheter from the sampling arm to the electromanometer. Arterial pressures were also recorded while blood sampling was not being carried out and although some of these records were damped, the majority were satisfactory and the pulse rate and rhythm were followed throughout the exercise and recovery

One member of the team was made specifically responsible for constant observation of the patient's condition and was empowered to stop the exercise at once if he thought fit. The patient was also instructed that, although he would probably be moderately breathless, he should stop at once, without hesitation, if he felt at all unwell.

Studies were performed on three main groups of patients who exercised at rates of work and oxygen consumption corresponding very approximately to walking on the flat at 3 m.p.h., 2 m.p.h., and 1 m.p.h.

TABLE II

Degree of dyspnoea and ventilation, M.V.B. saturation, cardiac output and vascular pressure changes

Subject	Degree of dyspnoea	Ex. vent. 5th min. (*L./min./m.*²*)	M.B.C. (*L./min./m.*²*)	$\frac{\text{Vent.}}{\text{M.B.C.}} \times 100$	Ex. level M.V.B. 5th min. (*% sat.*)	Mean pressures (*mm. Hg*) "Pulmonary capillary"	Resting P.A.	Ex. P.A.	Cardiac index (*L./min./m.*²) Resting	5th min. ex.
C1	none	9.1	48.1	15	55	22	26	30	4.21	6.17
C2	severe	15.8	29.8	53	35	26	30	66	3.44	7.99
C3	slight	16.8	54.3	31	18	28	35	65	2.12	3.49
C4	moderate	20.1	36.3	55	37	30	34	65	2.99	4.77
C5	slight	20.9	58.8	36	22	30	40	55	2.93	4.13
C6	none	12.2	37.8	37	31	26	32	66	2.59	3.28
C7	moderate	22.8	32.0	71	31	36	65	85	3.61	4.33
C8	moderate	10.5	37.2	28	29	38	48	—	2.83	2.77
C9	severe	21.1	35.2	61	21	33	50	83	3.02	3.30
C10	severe	25.6†	112.1	23	7†	40	62	80†	3.86	4.29
C11	moderate	13.7	25.3	54	37	38	55	75	2.84	3.32
C12	moderate	13.4	25.1	54	33	48	60	80	2.61	3.01
C13	slight	9.3	42.1	22	30	45	60	78	2.31	2.12
C14	moderate	7.2	22.3	32	37	26	40	82	2.56	2.25
C15	none	11.2	40.1	28	31	30	68	85	2.47	2.16
C16	moderate	12.1	39.8	26	9	48	55	64	1.39	1.66

* N.T.P.
† 4th min. values.

RESULTS

The results obtained are shown in Tables I and II and Figures 2, 3, and 5–9. In each of these figures the results in one or two normal subjects at the appropriate level of exercise are also shown. In Figure 2, illustrating the changes in mixed venous and arterial blood, each point plotted is the mean of two analyses of one sample of blood. Since blood samples were drawn at a steady rate it was considered justifiable to plot the percentage saturation of the sample at the mid-time of each collection. Abrupt changes in mixed venous blood could be plotted during rapidly changing states. It was possible from such records to calculate the mean (in time) arterio-venous oxygen content difference during each minute with considerable precision in the most variable states and, since the oxygen uptake during each minute was known, the cardiac output during that minute could be calculated. Transient differences in ventricular output cannot be appreciated by this method.

Sampling errors

Before discussing the findings obtained it is necessary to consider the possible errors that may have resulted from the use of the mean A–V difference (in time) and the oxygen uptake as determined by spirometry, during changing states, particularly in early exercise.

By plotting the percentage saturation of each steadily drawn mixed venous blood sample (10 seconds) at the mid-time of collection a curve will be obtained that represents the changing percentage saturation of the blood flowing through the pulmonary artery in relation to time. However the use of a mean A–V difference, derived from such a curve obtained with timed samples, in the Fick equation will only give an accurate calculated flow in changing states if *either* the flow *or* the A–V difference is constant over the minute period being studied (5). When both the flow and A–V difference are changing during the experimental period then the mixed venous blood saturation should be determined as each unit volume passes the point of sampling. The mean of such a series of observations would give a true mean A–V difference of the blood that has passed into the lungs which could be confidently applied to the Fick equation. Such a procedure is quite beyond present methods and knowledge; indeed, the problems being studied would have long been solved if pulmonary blood flow could be measured instantaneously and accurately.

The repeated demonstration of a steady mixed venous blood saturation and constant or nearly constant A–V difference after a period of exercise allowed the Fick principle to be applied with great confidence. It was shown, in seven of the sixteen patients studied, that no increase of cardiac output

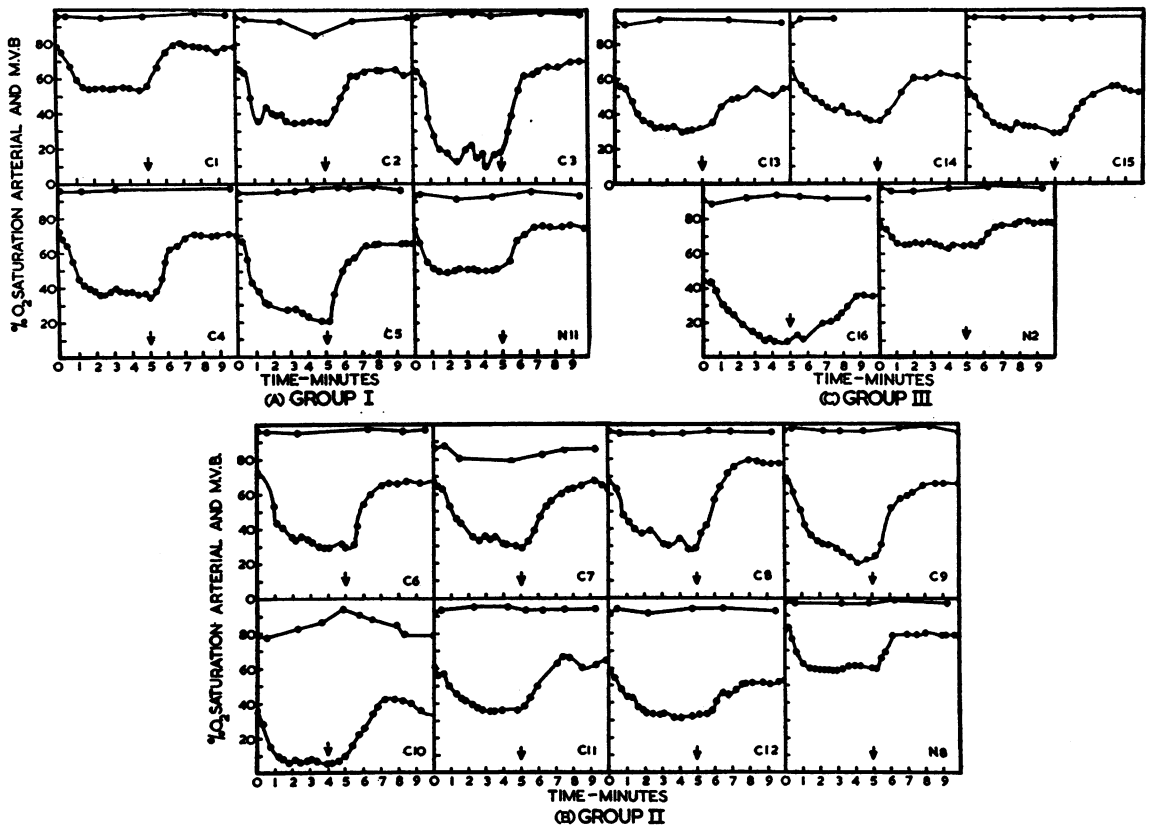

FIG. 2. ARTERIAL AND MIXED VENOUS BLOOD SATURATION DURING EXERCISE AND RECOVERY IN RHEUMATIC HEART DISEASE

C. Rheumatic heart disease. N, normal subject. Exercise commences at time 0, when resting values are plotted, and ends at signal. Max. oxygen uptake (ml./min./m². N.T.P.) Group I, 550 to 750. Group II, 360 to 490. Group III, 260 to 300.

occurred as judged by the resting steady state and exercise steady state determinations. It was considered, in these circumstances, most improbable that any increase in flow occurred during the unsteady state in early exercise and therefore, although the A–V difference was changing rapidly, the Fick principle could still be applied to timed samples without error. The fact that the cardiac output in early minutes of exercise, as calculated from timed samples, was equal to or very close to the values obtained in the resting and exercise steady states lent strong support to these theoretical considerations.

In six other patients the rise in cardiac output was so slight that, again, flow considerations were not important.

In Group I three patients showed a normal or almost normal rise of cardiac output on exercise, as judged by resting steady state and exercise steady state determinations, and it is of interest to estimate the order of error of calculated flows that resulted from the use of a mean A–V difference derived from timed samples in the first minute of exercise. An analysis, as suggested by Visscher and Johnson (5), of the errors in estimation of flow caused by the use of mean (time sampling) A–V difference over a period has been carried out on the data of the first minute of exercise in these three patients. As Visscher pointed out, the order of error of calculated flow with changing flow and A–V difference is a function of the ratios of flow and A–V difference during the two half-periods of the total period under consideration. In these three subjects the ratios of the half-minute mean A–V differences (time samples) could, with the present technique, be deter-

mined with some precision and they were as follows: patient C1, 1 : 1.48, patient C2, 1 : 1.29, patient C4, 1 : 1.44. The ratio of flow in the two half minutes was not known but a reasonable procedure to define the limit of error was to consider this ratio to be that of the resting cardiac output to the cardiac output in the second minute of exercise. In the three patients this ratio was as follows: C1, 1 : 1.40; C2, 1 : 1.51; and C4, 1 : 1.57. The calculated percentage error in flow determination resulting from the use of the minute mean A–V difference (in time) under these conditions was + 3 per cent, + 3 per cent, and + 4 per cent, respectively. These errors, although systematic, are of a lesser order than the differences between immediately repeated observations of the cardiac output in the resting steady state under the most rigidly controlled experimental conditions (4). Thus, even in these patients with a normal or nearly normal response to exercise, the error is apparently unimportant. While it is agreed that such errors must be carefully assessed it is also felt that the possible changes in flow and A–V difference and the sampling errors therefrom have been greatly overestimated.

Next the problem of the accuracy of the oxygen uptake determinations during rapidly changing states must be considered. As has been mentioned, the steady sampling of expired gas throughout each minute has again laid the investigators open to the errors that occur with "time sampling" when there are changes in both gas flow and oxygen extraction. The reasonably satisfactory checks shown in Figure 1 between what is in essence "time sampling" and "flow sampling" in this series is due to the almost constant oxygen extraction at all times in these patients with heart disease. Under such conditions, as pointed out

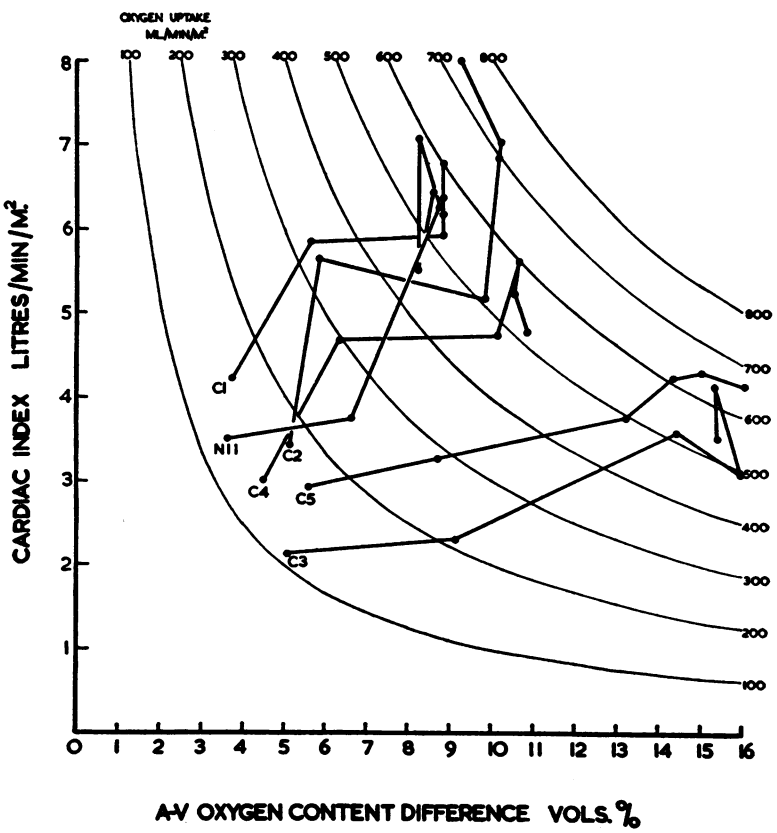

FIG. 3. A–V DIFFERENCE, CARDIAC INDEX AND OXYGEN UPTAKE AT REST AND DURING EACH MINUTE OF FIVE MINUTES EXERCISE GROUP I (C1–5, O_2 UPTAKE, 550 TO 750 ML./MIN./M².)

N, normal subject. All gas vols. at N.T.P.

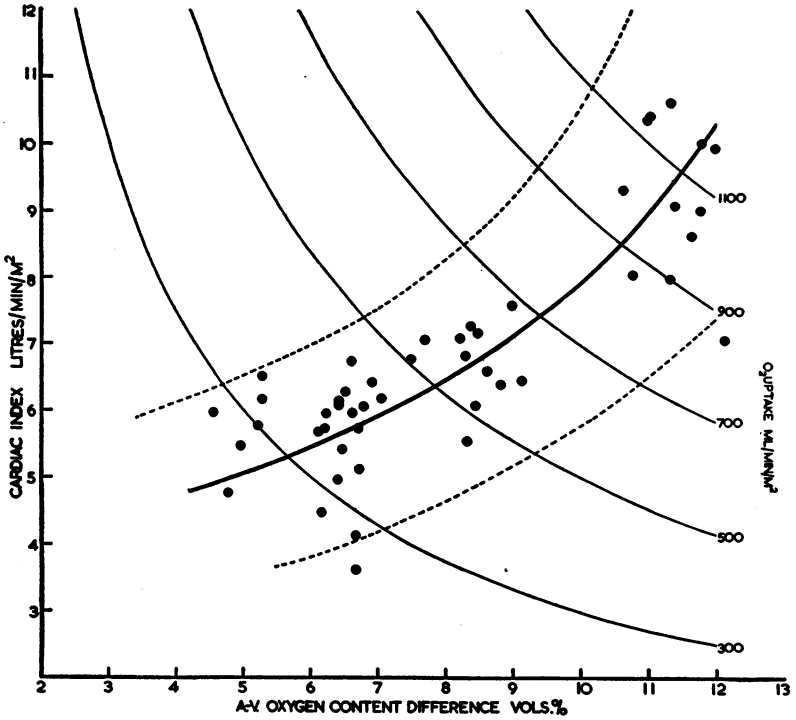

FIG. 4. A–V DIFFERENCE, CARDIAC INDEX AND OXYGEN UPTAKE DURING EXERCISE, AFTER STEADY STATE HAD BEEN ACHIEVED IN 16 NORMAL SUBJECTS

The third, fourth and fifth minute exercise results are plotted in each subject. Gas vols. N.T.P. Regression line and 95 per cent confidence limits shown are calculated from A–V difference/O_2 uptake relationships.

in relation to the Fick method, "time sampling" is almost as accurate as "flow sampling."

Even if the figures obtained were very close to the actual amount of oxygen that had been extracted from the expired air, there may have been further sources of error. The "spirometer oxygen uptake" may not be truly representative of the oxygen uptake by the blood in its passage through the lungs. A change in mean respiratory level of the chest and volume of air in the lungs during the early stages of exercise would cause such an error, as the volume of expired air collected would be appropriately altered. If the mean respiratory level and lung volume were reduced by a certain amount then this volume of gas entering the spirometer would cause a positive error of oxygen uptake estimation since its oxygen tension would not have reached these reduced levels by transfer of oxygen to blood during the experimental period. In the same way retention of inspired gas that had lost oxygen to the blood during the experimental period would cause a negative error. This possible change in respiratory level during exercise is most difficult to assess and is at present mainly a theoretical source of error. However, scrutiny of the data shows a low and relatively unchanging level of oxygen extraction in these patients with heart disease, even during early exercise, and it is of the order of 2.5 to 4.0 per cent in most cases. If the respiratory level changed by as much as half a litre then the resultant error in measuring "blood oxygen uptake" from "spirometer oxygen uptake" would only be 12 to 20 ml. and the error in cardiac output estimation with A–V differences of 5 to 10 vols. per cent would therefore be of the order of .02 L. per min. Such errors cannot be considered of importance.

Changes in the alveolar oxygen concentrations throughout the lungs in early exercise are another cause of difference between "spirometer" and "blood" oxygen uptakes. Approximate calcula-

tions of the changes of alveolar oxygen percentages between the resting state and the first minute of exercise, using the expired oxygen and carbon dioxide concentrations and assuming an effective tidal air of 75 per cent, gave the following results. In seven subjects the alveolar oxygen changed by less than 0.25 per cent, in five by 0.25 per cent to 0.5 per cent, in three by changes of between 0.7 per cent and 0.8 per cent and in one by 1.33 per cent. In ten cases the alveolar oxygen percentage was raised, in five lowered, and in one unchanged. If the lungs are assumed to have held two and a half liters of gas in the mid respiratory position then the resultant difference between "spirometer" and "blood" oxygen uptake in the first minute of exercise varied from 5 ml. (0.2 per cent change) to 25 ml. (1.0 per cent change) and in the majority of cases was below 10 ml. Again such errors will be of no importance with present techniques.

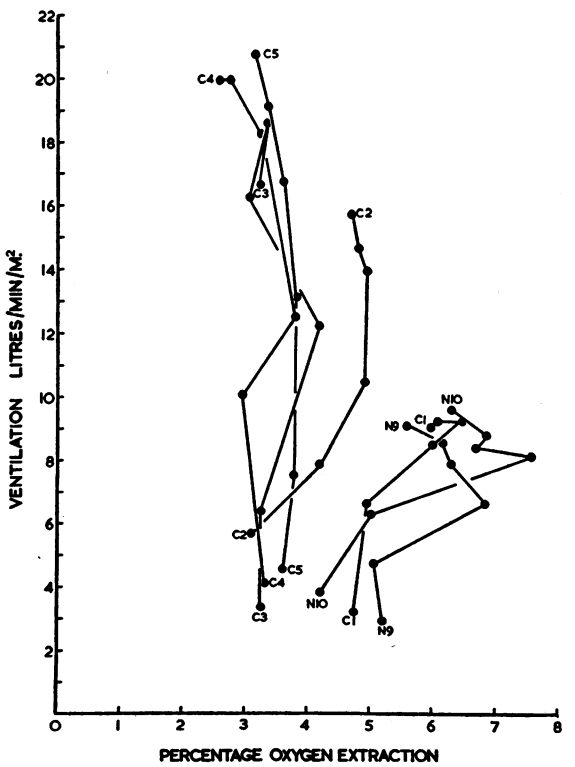

FIG. 5. VENTILATION AND PERCENTAGE OXYGEN EXTRACTION AT REST AND DURING EACH MINUTE OF FIVE MINUTES EXERCISE IN GROUP I (C1–5, O_2 UPTAKE, 550 TO 750 ML./MIN./M².)

N, normal subject. All gas vols. at N.T.P.

It has been suggested that imbalance between oxygen uptake by the blood in the lungs and body oxygen usage may cause inaccuracies when the Fick method is employed in changing states. It is difficult to see how such considerations affect the Fick principle when it is being applied only to the lungs and the blood flowing through them. Again, lag in changes in expired air in relation to blood oxygen uptake is unlikely to be very marked in view of the increased ventilation and respiratory rates of these subjects.

In summary, it can be stated that the errors resulting from time-sampling of the mixed venous blood during the changing state are of little importance in these studies of patients with heart disease. It has been shown that even with a normal response of cardiac output the errors caused by time sampling of mixed venous blood during early exercise are far less than the differences reported between repeated resting cardiac output estimations under ideal experimental conditions. A number of factors have combined to reduce errors in the estimation of the true oxygen uptake by the blood in the lungs during early exercise. However, in normal subjects with marked increase in oxygen extraction and fall in alveolar oxygen concentration during early exercise the difference between "spirometer" and "blood" oxygen uptake may cause significant errors of cardiac output estimation.

The steady state

There are obvious difficulties in defining a steady state when dealing with biological phenomena particularly when such a labile function as circulation is being considered. If the definition demanded that absolutely no change occurred in any of the parameters being measured, then a completely steady state would be a great rarity and in order for it to be demonstrated then either the techniques of sampling and analysis would have to be perfect or their errors absolutely constant. In this work the authors were specifically interested in the constancy or otherwise of the measurements that are employed to estimate the cardiac output by the Fick principle and it was considered that a steady state had been achieved when there was no important change or persistent trend of the oxygen uptake, arteriovenous difference or derived

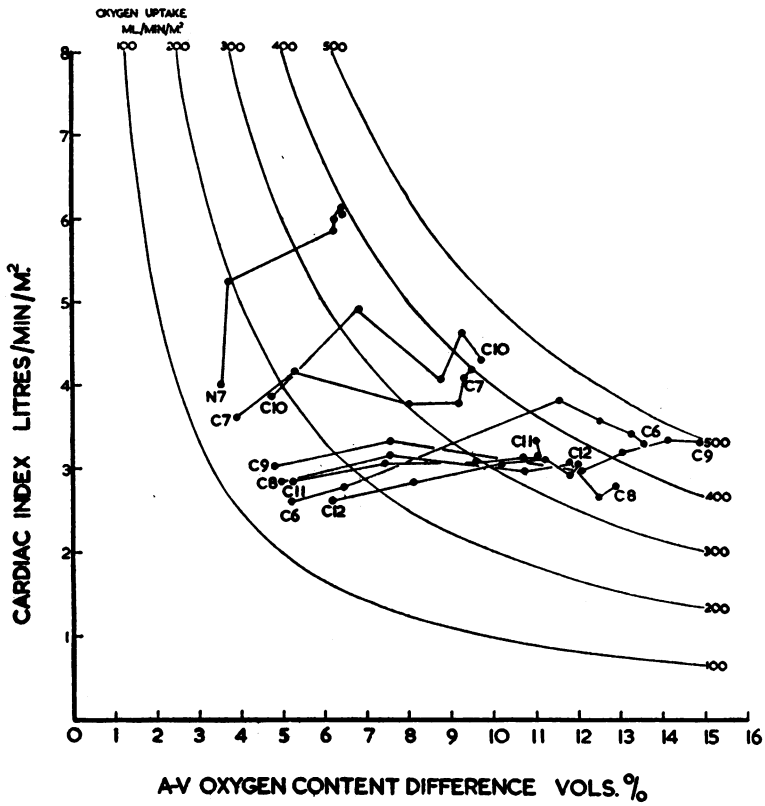

FIG. 6. A–V DIFFERENCE, CARDIAC INDEX AND OXYGEN UPTAKE AT REST AND DURING EACH MINUTE OF FIVE MINUTES EXERCISE GROUP II (C6–C12, O_2 UPTAKE 360 TO 490 ML./MIN./M².)

N, normal subject. All gas vols. at N.T.P.

cardiac output. This definition is inevitably open to slightly varying interpretations but this is not important to the main findings. In discussing the results the term steady state is therefore employed only in this special sense and its use does not imply constancy of ventilation, of heart rate, or of any measurements other than the oxygen uptake and A–V difference.

DISCUSSION OF RESULTS

Since the patients were divided into three groups, according to the level of work they could sustain for five minutes the main findings in each group will be discussed separately.

Group One

These patients were capable of considerable exertion and maintained a degree of exercise for five minutes that involved a maximum oxygen uptake of 550 to 750 ml. per min. per m² (N.T.P.) There were five patients in this group, four with mitral stenosis (C1, C2, C4, C5) and one with strong clinical evidence of mitral regurgitation as well as mitral stenosis (C3).

Mixed venous blood saturation during exercise and recovery (Figure 2A)

In the normal subject (N11), the mixed venous blood oxygen saturation fell from the resting figure (73 per cent) to a relatively steady level (50 per cent) in a little over one minute after the beginning of the same degree of exercise. On cessation of exercise there was a prompt recovery to the resting level in just over 90 seconds. The behavior of the symptomless patient with mitral stenosis (C1) was similar in all respects.

The more disabled patients all attained an abnormally low mixed venous blood oxygen saturation with this level of exercise, varying from 38 per cent to 17 per cent (normal 47 per cent to 54

per cent), (2) and although the fall in mixed venous blood saturation was precipitous, there was an appreciable delay in the achievement of a relatively even level of mixed venous blood saturation, particularly in C5 (M.S. Grade 3a).[2] On cessation of exercise, the mixed venous blood oxygen saturation returned to the resting level in the same time and therefore at an even greater speed than in normal subjects.

Cardiac output, A–V difference and oxygen uptake during exercise

In Figure 3 the derived cardiac index has been plotted against the A–V difference. As the oxygen consumption per square metre is the multiple of these two values a third series of curved coordinates showing various levels of oxygen consumption can also be constructed. The resting values of cardiac index and A–V difference in each case are first plotted, and the appropriate values obtained in the first to the fifth minutes of exercise are also plotted and joined by straight lines. Thus the behaviour of the cardiac index, A–V difference and oxygen consumption can be followed from minute to minute during five minutes exercise in each subject. For the purpose of comparison, Figure 4 shows the cardiac output plotted against the A–V difference after a steady state had been achieved during exercise in a study of 16 normal subjects by the authors. The regression line and 95 per cent confidence limits are also shown. All figures described as abnormal in this paper are outside these limits.

In the normal subject N11 (Figure 3) the resting cardiac index was 3.5 L. per min per m^2.; A–V difference 3.6 ml. per 100 ml. and oxygen uptake 125 ml. per min. per m^2. During the first minute of exercise the cardiac index increased to 3.7 L. per min. per m^2. the A–V difference to 6.6 ml. per 100 ml., and the oxygen uptake to 250 ml. per min. per m^2. The cardiac index, A–V difference, and oxygen uptake were relatively steady in the second, third, fourth, and fifth minutes of exercise, with a cardiac index of the order of 6.3 L. per min., A–V difference of 8.4 ml. per 100 ml., and oxygen uptake of 535 ml. per min.

[2] Grading of disability according to American Heart Association. See footnote to Appendix concerning subdivision of Grade 3.

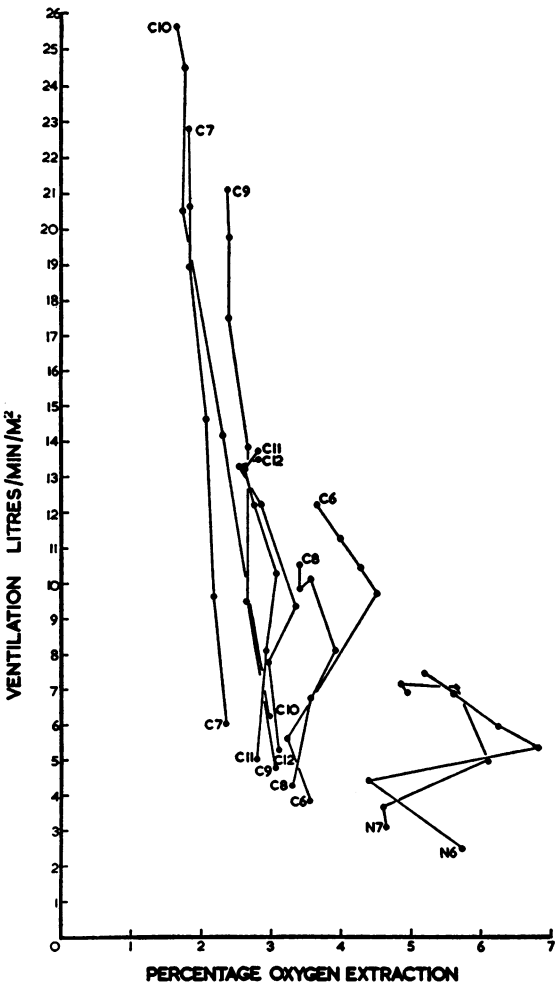

FIG. 7. VENTILATION AND PERCENTAGE OXYGEN EXTRACTION AT REST AND DURING EACH MINUTE OF FIVE MINUTES EXERCISE IN GROUP II (C6–C12, O_2 UPTAKE 360 TO 490 ML./MIN./M^2.)

N, normal subject. All gas vols. at N.T.P.

per m^2. In the study of normal subjects, of which N11 is typical, it was demonstrated that a steady state, as previously defined, was reached after one minute in all subjects exercising at levels comparable to those used in the present studies.

The patient C1 with symptomless mitral stenosis, behaved in a similar manner to the normal subject, achieving a steady state in the same time. C2 (M.S., Grade 2) showed what appeared to be a normal response of cardiac output and resultant A–V difference and came to an apparently steady state in the third and fourth minutes. In the fifth minute he developed frank pulmonary edema (the

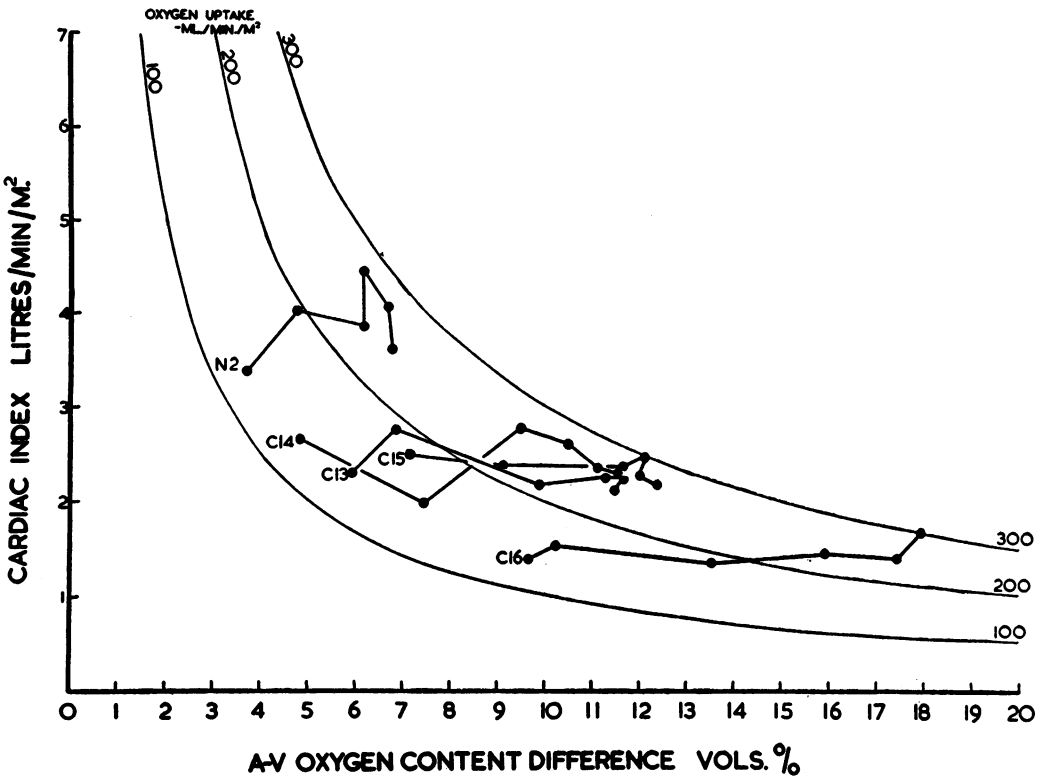

FIG. 8. A–V DIFFERENCE, CARDIAC INDEX AND OXYGEN UPTAKE AT REST AND DURING EACH MINUTE OF FIVE MINUTES EXERCISE, GROUP III (C13–C16, O_2 UPTAKE 260 TO 300 ML./MIN./M².)
N, normal subject. All gas vols. at N.T.P.

only instance of this in the series) and the arterial blood saturation fell to 86 per cent. The cardiac output then increased further, although the oxygen uptake remained almost constant. The signs and symptoms of pulmonary edema cleared rapidly with the cessation of exercise and the arterial blood saturation returned to its previous level (96 per cent) after five minutes recovery. C3 (M.S. and R., Grade 2) had a low resting cardiac index which rose but little on exercise with a resulting abnormal increase of A–V difference. Despite the abnormally low cardiac output and greatly increased oxygen extraction this patient achieved a relatively steady state *after* the second minute of exercise. C4 (M.S. Grade 3a) showed a slightly impaired rise of cardiac output and abnormal A–V difference (see Figure 4) and C5 a very slight increase of cardiac output and highly abnormal increase of A–V difference. C4 achieved a steady state *after* the first minute of exercise but C5, who showed but little increase of cardiac output, took two minutes to reach only a relatively steady state and was still increasing the A–V difference up to the end of exercise.

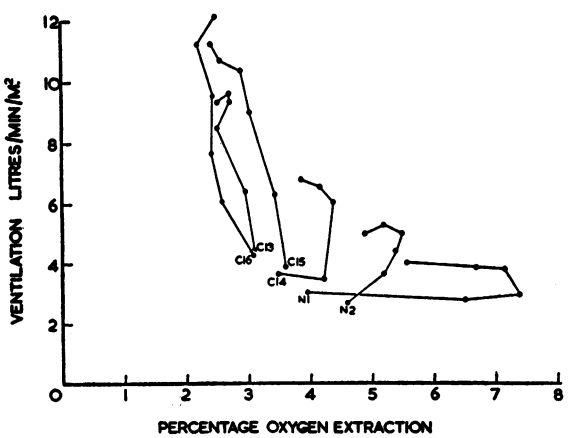

FIG. 9. VENTILATION AND PERCENTAGE OXYGEN EXTRACTION AT REST AND DURING EACH MINUTE OF FIVE MINUTES EXERCISE IN GROUP III (C13–C16, O_2 UPTAKE 260 TO 300 ML./MIN./M².)
N, normal subject. All gas vols. at N.T.P.

Ventilation and ventilatory equivalent during exercise

In Figure 5 the ventilation is plotted against the percentage oxygen extraction. The normal subjects N9, and N10 showed a considerable increase of oxygen extraction in the early minutes of exercise and, by the fifth minute, the extraction was returning towards the resting level and the ventilation was almost contant. The behavior of the ventilation and oxygen extraction in the patient with symptomless mitral stenosis (C1) was similar to that of the normal subjects. The remaining patients showed, on exercise, a marked ventilatory response with little change in oxygen extraction except in the case of C2 (Grade 2). Patients C2, and C5 were still increasing their ventilation considerably at the end of the five minutes exercise.

Group Two

The patients in this group were considerably disabled and were only capable of five minutes exercise involving a maximum oxygen uptake of 360 to 490 ml. per min. per m^2. (N.T.P.) There were seven subjects (see Appendix); four with mitral stenosis (C7, C8, C9, C10), one with mitral stenosis and regurgitation (C11), one with mitral stenosis and aortic stenosis (C12), and one with signs of predominant and severe mitral regurgitation (C6).

Mixed venous blood saturation on exercise and recovery

The behavior of the mixed venous blood saturation in these patients and in a normal subject (N8), performing the same degree of exercise is shown in Figure 2B. The percentage saturation of the mixed venous blood fell rapidly to an abnormally low level for this degree of exercise (28 per cent to 40 per cent; [3] normal, 55 per cent to 65 per cent). There was again some delay in achieving a relatively steady level of mixed venous blood saturation but all subjects had achieved this in two to three minutes with the exception of C9 (M.S., Grade 3b). There was an abrupt return to resting levels within 90 to 120 seconds of cessation of exercise, with only one exception (C10).

[3] C10 excepted.

C10 not only had mitral stenosis but was also anemic (Hb. 8.25 Gm. per 100 ml.), and consequently although the resting cardiac output was normal, the mixed venous blood percentage saturation was at the low level of 37 per cent. On exercising the combination of anemia, and the inability to raise the cardiac output normally, caused a fall of mixed venous blood percentage saturation to the astonishing figure of 6 per cent. (Figure 2B). This patient had to stop exercising after four minutes owing to very severe dyspnoea and there was a considerable delay in recovery of mixed venous blood oxygenation to the resting level. The mixed venous blood saturation finally rose above the resting level, and fell again to that level. This phenomenon was almost certainly due to the fact that this patient was suffering from arterial blood desaturation at rest (79.6 per cent), achieved relatively normal saturation at the end of exercise and during early recovery (92.7 per cent), and then returned to the previous arterial saturation (78.7 per cent). This odd behavior of arterial oxygenation on exercise has been observed in other anemic subjects without heart disease.

In the case of C12, the catheter tip would not remain in the pulmonary artery and atrial samples were collected throughout. The return of the mixed venous blood saturation to a level considerably below the resting level may have been due to the vagaries of atrial sampling and the figures in this case must be viewed with some reserve. Similarly, in the study of C8 (M.S., Grade 3b) the tip of the catheter slipped back into the right atrium during exercise. The mixed venous blood saturation rose on recovery to well above the resting level and this rise was sustained to the end of the study. If these figures were accepted then it would appear that, although this patient was unable to raise the cardiac output on exercise, there was a significant increase during recovery. Again it is possible that this unusual finding is due to the uncertainties of atrial sampling.

Cardiac output, A-V difference, and oxygen uptake during exercise (Figure 6)

In a normal subject (N7), performing the same degree of work, the increase of oxygen uptake was effected by an approximately 50 per cent increase in cardiac output and a doubling of the A–V dif-

ference. The rapid achievement of the steady state, as measured by these values, *after* the first minute is also shown.

The behavior of the patients with heart disease contrasted with the normal subjects even more strikingly than in the previous group. The majority showed no ability to increase the cardiac output as oxygen uptake increased, the A–V difference increasing almost proportionately to the oxygen uptake. This was best shown in cases C8 (M.S., Grade 3b), C9 (M.S., Grade 3b), C11 (M.S. and R., Grade 3b) and C12 (M. and A.S., Grade 4), all of whom had low resting cardiac outputs. Despite the fixed cardiac output and abnormally increased A–V difference, C8, C11, and C12 reached a steady state *after* two minutes but C9 (M.S., Grade 3b) still showed an increase of oxygen uptake and A–V difference up to the fifth minute of exercise. C6 (M.R.), a patient with Grade 2 disability and the only member of the group to suffer no dyspnoea at this level of exercise, had a resting cardiac index as low as the severely disabled patient (C12) with severe mitral stenosis and aortic stenosis. In the first two minutes of exercise the cardiac output increased by 50 per cent but during the third, fourth, and fifth minutes, although the oxygen uptake remained constant, there was a slight but steady fall of cardiac output and increase of A–V difference. In patients C7 (M.S., Grade 3b) and C10 (M.S., Grade 3b) the cardiac output was normal at rest and showed a transient rise on exercise, which was not sustained, the A–V difference increasing abnormally with increase of oxygen uptake. Both subjects achieved a steady state *after* the second minute of exercise.

Ventilation and ventilatory equivalent during exercise

These patients showed a higher resting ventilation and lower oxygen extraction than normal subjects. In this small group there is quite a striking correlation between the degree of disability and the elevation of the resting ventilation and the ventilatory response to exercise. Those with the highest resting ventilation and lowest oxygen extraction showed the greatest ventilatory response (Figure 7). The ventilatory response of two normal subjects (N6 and N7) to the same degree of exercise is also shown.

Four patients C6, C7, C9, and C10 showed an increasing ventilation throughout the exercise period. Patients C8, C11, and C12 reached a steady level of ventilation and oxygen extraction in the last two or three minutes of exercise. The oxygen extraction was almost constant even during early exercise, except in the relatively fit patient C6 (Grade 2).

Group Three

The four patients in this group were all severely disabled, (Grade 3b or 4). Two of the patients had mitral stenosis (C14, C15), one had mitral stenosis with gross regurgitation (C13), and one had severe mitral and aortic stenosis (C16).

Mixed venous blood percentage saturation during exercise and recovery (Figure 2C)

During this very slight exertion, which must be paralleled not infrequently in everyday life even under the most restricted conditions, the mixed venous blood oxygenation in these patients reached very low levels. Patient C14 (M.S., Grade 3b) and patient C16 (M. and A.S., Grade 4) showed great delay in reaching a steady mixed venous blood saturation and, although the levels of percentage saturation reached by these two patients were very different (36 and 8 per cent), they appear to approach a constant level at the end of exercise. When the exercise ceased the oxygen saturation of the mixed venous blood did not regain its resting level in C13 (M.R., Grade 3b) or C15 (M.S., Grade 4) for three minutes and the recovery was not complete in five minutes in patient C16 (M. and A.S., Grade 4). There was no marked change in arterial blood saturation on exercise in this group.

Cardiac output A–V difference and oxygen uptake during exercise (Figure 8)

The behavior of a normal subject N2 at this level of exercise indicates that although there is a relatively steady state *after* one minute's exercise, there is still considerable "seeking." This may be due to the fact that normal subjects find this very light leg work rather unnatural and difficult to maintain at a steady level. Some normal subjects, who had a slightly raised resting cardiac output and small A–V difference due to some de-

gree of nervous tension, did little more on exercising at this level than increase their A–V difference (2).

All four patients had resting cardiac indices below 3 L. per min. per m^2. and the patient with aortic and mitral stenosis (C16) had a resting cardiac index of 1.39 L. per min. per m^2. On exercise, none of these patients showed any increase of cardiac output and in patients C13 (M.R.), C14 (M.S.), and C15 ,M.S.) the final cardiac output was slightly less than in the resting state. In all cases, therefore, the A–V difference increased almost proportionately to the increase in oxygen uptake.

As judged by these measurements C15 (M.S., Grade 4) achieved a remarkably steady state *after* one minute and C13 (M.R., Grade 3b) *after* two minutes. C14 (M.S., Grade 3b) did not achieve such a steady state and although the oxygen uptake was almost constant after the first minute of exercise, the cardiac output was decreasing and the A–V difference increasing in the fifth minute. C16 (M. and A.S., Grade 4) with the very low cardiac output, showed an abnormal, and increasing A–V difference from the first to the fifth minute.

Ventilation and ventilatory equivalent (Figure 9)

In three of these patients the exercise ventilation was greatly increased as compared with the normal subjects. One of these patients, C13, had reached a steady level of ventilation after the second minute but in the others it was still increasing in the fifth minute of exercise, with decreasing oxygen extraction. Patient C14 (M.S., Grade 3b) had only moderately increased ventilation and showed increased oxygen extraction during the first three minutes of exercise, behavior more like that of a normal subject.

Behavior of A–V Difference and Cardiac Output during Recovery in All Groups

In the early stages of this study the oxygen uptake was only determined in the second and fifth minute of recovery, but minute to minute recovery studies were made in nine patients. The behavior of normal subjects during recovery after five minutes exercise at comparable levels was remarkably constant (2). Immediately after exercise ceased the cardiac output, A–V difference and oxygen uptake fell rapidly and, by the second minute of recovery, these values were very close to, if not at, the pre-exercise values, which they invariably achieved in the third minute of recovery.

In all of the cardiac patients the mixed venous blood saturation had returned to pre-exercise levels by the second minute of recovery with the exception of patients C12 and C16, both of whom had aortic stenosis in addition to mitral stenosis. Despite this the A–V difference remained increased in many subjects up to the fifth minute of recovery, partly because the blood oxygen capacity was assumed to remain at its increased exercise level during this time and partly because ventilation remained considerably increased thus causing a slight rise of the arterial blood saturation during early recovery.

In those patients in whom the cardiac output rose considerably on exercise the rate of return to the resting output level was normal in patients C1 (Grade 1) and C4 (Grade 3a) and probably slightly delayed in patient C2 (Grade 2). In the six patients with only a slight rise of cardiac output on exercise, the output returned to its pre-exercise level by the third minute of exercise in only two patients, C5 (Grade 3a) and C6 (Grade 2), neither of whom was very disabled. In patient C3 (Grade 2) who was not very disabled but had recently been in failure, the return of the cardiac output to resting levels was not complete by the fifth minute of recovery. A secondary rise of cardiac output occurred during recovery in patients C7, C8, and C10 (all Grade 3b) and this delayed the return to resting levels until at least the fifth minute of recovery. No explanation can be given for this secondary rise but in patient C8 the finding may have been due to the errors of atrial sampling. In the remainder of the patients (all Grades 3b and 4) the cardiac output remained constant throughout exercise and recovery but in all cases the A–V difference remained elevated until the fifth minute of recovery, this being most marked in patient C16 in whom it was still almost a third above the resting value in the fifth minute of recovery. In all patients the ventilation was still increased in the fifth minute of recovery and in many, especially in those performing the highest level of exercise, this increase was considerable.

Pulse Rate and Stroke Volume during Exercise and Recovery

The pulse rate increased during exercise in all subjects. Eight of the patients achieved a steady rate after the second minute and three after the third minute of exercise. Rather surprisingly, three patients with auricular fibrillation and "fixed" cardiac outputs achieved a constant pulse rate after the first minute of exercise. Two very disabled patients increased their pulse rate throughout although one achieved a very steady oxygen uptake, cardiac output and A–V difference after two minutes (C13). In some patients the pulse rate was steady before the cardiac output and A–V difference stabilized and in other patients after. In three instances a constant pulse rate was achieved although the patients never reached a steady state as judged by oxygen uptake, cardiac output and A–V difference. These findings show that constancy of pulse rate is not a reliable criterion of steadiness of the A–V difference and cardiac output.

The heart rate was slow to return to resting levels after exercise and in many subjects had not returned to pre-exercise levels by the fifth minute of recovery, especially in the group performing the heaviest exercise.

The stroke volume fell during exercise in all subjects except C1 and C2, although C10 and C13 showed a small transient increase during the first minute. A steady level of stroke volume was achieved at least during the second minute of exercise and in several cases during the first minute. Although stroke volumes are given in all studies these figures are of little value in the patients with auricular fibrillation. Stroke volumes were lower in the fifth minute of recovery than before exercise in the majority of the subjects.

Respiratory Quotient during Exercise and Recovery

In all these patients the respiratory quotient (R.Q.) was almost constant in the fourth and fifth minutes of exercise and in some patients by the third minute. In the majority of patients who achieved a steady A–V difference and cardiac output, the R.Q. did not stabilize until a minute or two later. However in three patients (C5, C9, C16), who did not achieve a constant A–V difference and cardiac output, the R.Q. reached a nearly constant value in the last two or three minutes of exercise. In many instances a fall of the R.Q. occurred during the first one or two minutes of exercise but this was never marked and of a lesser order than in normal subjects under the same conditions. In those patients performing the lightest work there was little change of the R.Q. during exercise, except in C15. In all patients in all groups, with the exception of C2, the final exercising R.Q. was higher than the resting value.

During recovery, with continued high ventilatory volumes and rapid fall of oxygen uptake, nearly all subjects showed a further rise of R.Q. to well over unity, and in several cases to very high values (C10, 1.44 and C5, 1.71). Only subjects C8, C9, and C11 showed any re-establishment of a steady R.Q. during the recovery study, this being in the fourth and fifth minute of recovery, yet the majority of patients had returned to a steady near-resting cardiac output and A–V difference towards the end of five minutes recovery. These observations indicate that it is unwise to infer the degree of steadiness of the cardiac output and A–V difference from the constancy or otherwise of the respiratory quotient.

Oxygen Uptake and Oxygen Debt

The present observations demonstrate the difficulty in obtaining constancy of oxygen uptake during exercise even under carefully controlled conditions. Also, a steady oxygen uptake during exercise does not necessarily mean that a steady A–V difference and cardiac output have been achieved. Subjects C2, C6, and C14 all showed changing cardiac outputs and A–V differences although the oxygen uptake had become constant (see Figures 3, 6, and 8).

As the recovery studies were incomplete in a number of subjects and, in any case, were only continued for five minutes, useful data concerning the oxygen debt are possible in only a few instances. Normal subjects carrying out similar exercise to the patients in Group I, involved oxygen debts of about 15 per cent of the total excess oxygen consumption and this was almost completely "paid off" during the first minute of recovery. Patients C3 and C5 had oxygen debts

of the order of 22 per cent and 28 per cent of excess oxygen consumption, of which only half was paid off in the first minute and the rest more slowly.

At the level of exercise of the second group, normal subjects incurred an oxygen debt of 12 to 15 per cent of the total excess oxygen consumption, which they paid off almost completely in the first minute of recovery. Patient C6 showed a 24 per cent oxygen debt and paid off only 8 per cent in the first minute, patient C10 a 29 per cent oxygen debt of which 13 per cent was paid off in the first minute, and patient C11 a 20 per cent oxygen debt of which only 5 per cent was paid off in the first minute of recovery. All three patients had returned to the resting level of oxygen uptake by the fifth minute of recovery.

Finally, only patient C1 (asymptomatic mitral stenosis) in the first group, five of the seven in the second group, and three of the four in the third group had returned to the resting level of oxygen uptake by the fifth minute of recovery. Summarizing, it was confirmed that patients with heart disease showed an increased and prolonged oxygen debt as compared with normal subjects.

Oxygen Transfer in Lungs and Tissues

As already reported by many workers the resting arterial blood saturation is normal or nearly normal in the large majority of patients with rheumatic heart disease even in the later stages when the patient has been repeatedly in congestive failure. In the present series the arterial saturation was 94.8 per cent or above in all those capable of the highest grade of exercise (Group I, C1–5). In four of these patients the arterial saturation was maintained during exercise and rose significantly after exercise while increased ventilation was continued. The one exception in this group was the patient who developed pulmonary edema and whose arterial saturation fell from 96.6 per cent to 86 per cent returning to the original level after five minutes recovery.

In Group II (C6–C12), three patients (C6, C8, C9) had normal resting arterial saturation which behaved in the same manner on exercise as in Group I. Patients C11 and C12 who were the most disabled in this group, had a slightly lower arterial saturation 90.7 per cent and 92.0 per cent, respectively, but both improved their arterial blood saturation slightly during exercise and recovery. Patient C7 (M.S., Grade 3b) who had a resting arterial saturation of 86.9 per cent which fell to 80.2 per cent on exercise, had no history of asthma or respiratory infection and is a good example of how moderate arterial desaturation can occur in a patient with mitral stenosis whose past history is in no way exceptional. Carroll, Cohn, and Riley (6) have demonstrated disturbance of both gas and blood distribution and of the diffusing capacity of the lungs in mitral stenosis but, as yet, there appears to be no definite explanation of the mechanisms involved or of their apparently fortuitous occurrence. Patient C10, exceptional in that he was anemic as well, showed considerable arterial desaturation at rest, which disappeared on exercise, and returned during recovery.

In Group III, there was slight arterial desaturation (92.7 per cent, 91.1 per cent, 91.3 per cent) in three instances, the arterial saturation improving considerably on exercise and during recovery. One patient had normal arterial blood oxygenation throughout.

Despite the marked and long standing rise of vascular pressures throughout the lungs, the transfer of oxygen to the blood passing through them remained efficient in the majority of these patients. Normal arterial saturation was maintained even when the mixed venous blood was returning to the lungs at levels of oxygen saturation of between 6 per cent and 20 per cent. The oxygen transfer in these patients is, however, aided by several factors. The hyperventilation at rest and during exercise causes a significant rise of the alveolar oxygen tension even if there is some faulty gas distribution. This, combined with the very low oxygen tension of mixed venous blood, results in a greatly increased oxygen diffusion gradient. The low cardiac output at rest and on exercise is also associated with a relatively low blood flow velocity through the pulmonary capillaries and a corresponding increase in the time of exposure to the blood-gas interface.

Although it has long been known that cardiac and skeletal muscle is capable of functioning at low levels of oxygen tension, it has not been appreciated, at least by the authors, that striated muscle can continue to function and utilize considerable quantities of oxygen at the low levels of

oxygen tension which must have been present in the muscles of some of these patients in whom the mixed venous blood was returning to the heart less than 10 per cent saturated during exercise. The rapid rise of the oxygen saturation of the mixed venous blood after exercise would suggest that a marked "alactic acid" oxygen debt does not occur even at these low oxygen tensions, as the recovery would not be so rapid unless the local muscle oxygen demands ceased almost immediately after the end of exercise.

Dyspnoea on Exercise

Patients with heart disease have considerable difficulty in describing their symptoms while under stress. They may state that they are extremely short of breath without other symptoms, or may describe weakness, either generalized or in the exercising legs. Others report unpleasant sensations of physical inadequacy or even apprehension. A few patients will under no circumstances increase their activity over a certain level and look under obvious stress, yet will deny shortness of breath or weakness. No patient in this series with predominant mitral involvement complained of anginal pain, precordial discomfort or palpitations.

In Table II the degree of dyspnoea, as described by the patient, is shown with the maximum breathing capacity (7) and the ventilation in the last minute of exercise. The fifth minute ventilation is also expressed as a percentage of the maximum breathing capacity. Although there is a rough correlation between the percentage of the ventilatory capacity used and the degree of dyspnoea there are many individual exceptions. Patient C7 who used 71 per cent of the ventilatory capacity was only moderately dyspnoeic. Such a finding could be due to a well disguised lack of cooperation in the maximum breathing capacity determinations, but this would not explain the finding in patient C10 who was extremely dyspnoeic while using only 23 per cent of his ventilatory capacity. These limited observations are in agreement with the extensive ventilatory investigations in mitral stenosis by Frank, Cugell, Gaensler, and Ellis (8).

There was no correlation of dyspnoea with the level of mixed venous blood oxygenation achieved during exercise; C11 and C14, with a mixed venous blood saturation of 37 per cent, suffered moderate dyspnoea yet patient C3, with a mixed venous blood saturation of 17.5 per cent, was only slightly dyspnoeic. Patient C15 with a mixed venous blood saturation of 31 per cent had no shortness of breath and patient C16 suffered only moderate dyspnoea and could have continued the exercise for a longer period although the oxygen saturation of the mixed venous blood had fallen to 9.5 per cent.

Shortness of breath was studied in relation to the degree of, or lack of, increase of cardiac output on exercise. Neither dyspnoea nor ventilatory response appeared to be related to the response of the cardiac output (Table II). Similarly, no consistent relationship could be found between the ventilatory response or degree of dyspnoea and the resting pulmonary artery pressure, the resting transpulmonary pressure (P.C.P.), or the degree of rise of pulmonary artery pressure on exercise (Table II).

Regional Blood Flow Considerations

Although it was anticipated that the oxygen saturation of mixed venous blood of these patients with heart disease would fall to abnormally low levels on exercise, the extent of this fall, in some cases to levels of 6 to 10 per cent saturation, was a considerable surprise. These low figures on exercise suggested that a very marked redistribution of the flow of blood throughout the body must have occurred and it seemed likely that besides a reduction of the renal and splanchnic flow there was also a marked reduction of blood flow to the upper part of the body. The relative constancy or even elevation of the systemic blood pressure on exercise in patients who were unable to increase their cardiac output also suggested that there was widespread vaso-constriction in non-exercising zones. Work proceeds on this problem, as the technique evolved can also be used to follow the behavior of the A–V difference in various regions of the body with considerable precision during exercise and recovery or any other changing state. It has already been shown conclusively that during leg exercise in these disabled patients the oxygen content of the superior vena caval blood falls considerably and that the axillary vein blood of the non-exercising arms may

fall to even lower levels of saturation than the mixed venous blood in the pulmonary artery. When exercise ceases there is a prompt return of the percentage saturation of the axillary vein blood to the resting level. As it is unlikely that the oxygen uptake of the resting arm increases significantly during leg exercise, this demonstration of a greatly increased arteriovenous oxygen content difference in the arm is a strong indication that vasoconstriction has occurred in the limb with marked reduction of blood flow. Preliminary plethysmographic studies have confirmed that there is considerable reduction in muscle blood flow in the non-exercising arms of these patients during light exercise. The oxygen content of blood sampled from the cranial end of the jugular vein remains unchanged throughout such exercise even in gravely disabled subjects. These studies of the changes of regional A–V differences and blood flow in normal subjects and patients with heart disease during exercise are being reported in detail in another communication.

Findings in Relation to Standard Sampling Procedure

Ten of these sixteen subjects, who were exercising at different levels, but fairly near their tolerance, reached a steady state of oxygen uptake, A–V difference and cardiac output in 2 to 3 minutes. The six remaining subjects did not achieve a steady state in five minutes. One of these six patients developed pulmonary edema and need not be considered further. Three, although they had not quite reached a steady state, as judged by minute to minute studies, had actually achieved a steady level of arterial and mixed venous blood saturation by the fifth minute of exercise. In only two subjects, C5 and C14, the mixed venous blood saturation failed to reach a steady level, continuing to fall slightly up to the end of exercise. As neither patient was unduly embarrassed it is likely that they would have reached a steady state if exercise had continued. There appeared to be no important common feature in the patients who showed a considerable delay in achieving a steady state.

From consideration of these results, it would appear that "spot" samples taken in the fifth minute of exercise would have given A–V differences and cardiac outputs that would have been representative of the final steady hemodynamic state in all but two patients. Although it is impossible to be certain, it is most likely that even in these two cases the results obtained from "spot" fifth minute samples would not have been far from those of the final steady state. The occasional variation of mixed venous blood saturation around a particular level even when the patient is in an almost steady state emphasizes the need for taking at least three evenly spaced samples over the minute of study. It is also advisable to confine the collection of expired air to the period of mixed venous blood sampling.

SUMMARY

A technique has been developed whereby the behaviour of the mixed venous and arterial blood saturation can be followed accurately during rapidly changing states. It has thus been possible to determine the minute to minute changes of cardiac output in patients with rheumatic heart disease during five minutes exercise and the subsequent recovery.

Errors in cardiac output determination during early exercise due to the use of mean (in time) A–V differences and the difficulty of measuring true blood oxygen uptake are shown to be of such a small order in these studies that they are of no importance.

Particular study has been made of the rate of achievement of a steady state after the commencement of exercise. In ten out of sixteen patients a steady state of oxygen uptake, A–V difference and cardiac output was achieved after two to three minutes. A number of exceedingly disabled patients who were unable to raise their cardiac output on exercise and had very abnormally increased A–V difference reached a steady hemodynamic state in a few minutes.

The constancy of the ventilation, respiratory quotient, pulse rate and oxygen uptake were all found to be unreliable criteria of the steadiness of the cardiac output.

The mixed venous blood saturation fell to exceedingly low levels in a number of patients who were, however, able to continue to exercise without undue distress for several minutes. In most cases, there was a remarkably prompt recovery

of the mixed venous blood saturation to resting levels after the exercise stopped.

There appeared to be no correlation between the degree of dyspnoea and the ventilation, either in absolute terms or expressed as a percentage of the maximum breathing capacity. Similarly no important relation was found between the degree of dyspnoea and the level of mixed venous blood saturation, the behavior of the cardiac output, the pulmonary artery pressures, or the resting transpulmonary pressures (P.C.P.)

Brief mention is made of evidence suggesting that there is considerable reduction of blood flow to the upper body, especially to the arms, when these disabled patients exercise.

ACKNOWLEDGMENTS

Grateful acknowledgment is made to Dr. G. Cumming and Staff Nurse E. M. Dalton for help in a number of these studies and also to Mr. R. J. Mills for excellent technical assistance. We are indebted to grants from the Endowment Research Fund of the United Birmingham Hospitals and from Messrs. Imperial Chemical Industries Ltd.

APPENDIX

Details of Subjects

Group One

C1. Male. Aged 25. S.A. 1.68 m². Mitral stenosis. Disability Grade I.[4] No symptoms except acute cardiac neurosis seven days before admission when suddenly told he had "serious heart disease."

Normal sized heart. Sinus rhythm. Classical signs of mitral stenosis. *Fluoroscopy:* left atrium normal.

C2. Male. Aged 43. S.A. 1.60 m². Mitral stenosis. Disability Grade 2. Dyspnoea two and one-half years ago, gradually increased. Several severe attacks nocturnal dyspnoea during last year. No hemoptysis or edema.

Heart moderately enlarged. Sinus rhythm. Classical signs of mitral stenosis, slight aortic incompetence. *Fluoroscopy:* left atrium not enlarged. *Operation:* moderate mitral stenosis, no regurgitation.

C3. Female. Aged 42. S.A. 1.60 m². Mitral stenosis and regurgitation. Disability Grade 2. Attacks of paroxysmal tachycardia since 18. Otherwise no symptoms until 10 months ago. After sore throat developed shortness of breath and ankle edema, progressing to frank congestive failure. Rapid recovery, now has excellent exercise tolerance. No hemoptysis.

Heart considerably enlarged. Auricular fibrillation. Signs of mitral stenosis and regurgitation. Slight aortic incompetence. *Fluoroscopy:* left atrium and both ventricles enlarged.

C4. Female. Aged 23. S.A. 1.49 m². Mitral stenosis. Disability Grade 3a. Onset of dyspnoea one year ago, gradually increasing. Occasional hemoptysis last year. No edema.

Heart not enlarged. Sinus rythm (intermittent auricular fibrillation). Classical signs of mitral stenosis with slight aortic incompetence. *Fluoroscopy:* left atrium enlarged. *Operation:* mitral stenosis, no regurgitation.

C5. Male. Aged 34. S.A. 1.61 m². Mitral stenosis. Disability Grade 3a. Laborer's work until two months ago without symptoms, then dyspnoea on exertion and mild ankle edema on several occasions. No frank congestive failure. No hemoptysis.

Heart greatly enlarged. Auricular fibrillation. Moderate mitral systolic and loud mid-diastolic murmur. *X-ray:* left atrium greatly enlarged. *Operation:* moderate mitral stenosis no regurgitation.

Group Two

C6. Female. Aged 36. S.A. 1.52 m². Mitral regurgitation. Disability Grade 2. Some dyspnoea since childhood with slight deterioration recently. Considerable variation. No edema or hemoptysis at any time.

Heart moderately enlarged. Sinus rhythm. Left ventricular impulse increased with right ventricular thrust. Loud systolic murmur conducted backwards and soft mid-diastolic murmur in mitral area. No aortic murmurs. *Fluoroscopy:* large left atrium with systolic expansion. Left ventricle enlarged but right ventricle more so. Calcified mitral valve. Considerable mitral regurgitation considered present. Operation not advised.

C7. Female. Aged 35. S.A. 1.58 m². Mitral stenosis. Disability Grade 3b. Dyspnoea ten years with considerable deterioration last two years. Two slight hemoptyses recently. No edema.

Heart slightly enlarged. Sinus rhythm. Classical signs of mitral stenosis. *X-ray:* left atrium enlarged. *Operation:* considerably stenosed, funnel shaped mitral valve.

C8. Female. Aged 44. S.A. 1.61 m². Mitral stenosis. Disability Grade 3b. Disability heralded by attack of congestive failure five years ago. No edema or hemoptysis since but has remained severely disabled by dyspnoea.

Heart considerably enlarged. Sinus rhythm. Classical signs of mitral stenosis with soft apical systolic murmur and slight aortic incompetence. *X-ray:* big heart, predominantly right ventricle. Left atrium also enlarged. *Operation:* very severe mitral stenosis.

C9. Female. Aged 24. S.A. 1.45 m². Mitral stenosis. Disability Grade 3b. First noticed slight dyspnoea 10

[4] The clinical grading of disability used here is in accordance with that of the American Heart Association, except that Grade 3 is considered by the authors to be too wide, as it includes all degrees of disability between slight discomfort with normal activities, to discomfort at rest. It has, therefore, been subdivided into Grades 3a and 3b. Patients with Grade 3a disability are able to walk a mile or more on the flat at their own speed and can ascend stairs slowly without undue discomfort. Many such patients can still earn a livelihood or perform most household tasks.

years ago. More severe last four years with considerable deterioration in last nine months. No edema or hemoptysis.

Heart very slightly enlarged. Sinus rhythm. Classical signs of mitral stenosis. *X-ray:* Heart slightly enlarged due to right ventricular hypertrophy. *Operation:* severe mitral stenosis, no regurgitation.

C10. Male. Aged 34. S.A. 1.59 m^2. Mitral stenosis. Disability Grade 3b. Some dyspnoea 10 years ago on violent exertion when successful paratrooper. Increased slowly since, but more rapid deterioration last three years and especially last six months. Several attacks of severe nocturnal dyspnoea recently and hemoptysis once. No edema. Anemic (Hb. 8.25 Gm. per 100 ml.)

Heart only slightly enlarged. Sinus rhythm. Classical signs of mitral stenosis. Soft aortic diastolic murmur. *X-ray:* heart within limits of normal but pulmonary conus enlarged. *Operation:* delayed 9 months for possible subacute rheumatism to subside. Anemia responded to iron treatment. Severe mitral stenosis found, no regurgitation.

C11. Female. Aged 28. S.A. 1.46 m^2. Mitral stenosis and regurgitation Disability Grade 3b. Dyspnoea commenced five years ago. Two years ago "pneumonia" and has deteriorated rapidly since. Severe nocturnal dyspnoea and hemoptysis. No edema.

Heart considerably enlarged. Auricular fibrillation. Mitral systolic murmur conducted backwards with rumbling diastolic murmur *X-ray:* left atrium enlarged considerably. *Operation:* mitral valve stenosed and calcified with considerable regurgitation.

C12. Male. Aged 30. S.A. 1.68 m^2. Mitral and aortic stenosis. Disability Grade 4. Well until year ago when developed congestive cardiac failure with severe recurrent pulmonary infarction. Recurrent congestive failure since. No edema at time of study, although venous pressure raised. Hemoptysis related to pulmonary infarction.

Large heart, right and left ventricular enlargement. Auricular fibrillation. Soft mitral systolic and mid-diastolic murmurs. Marked aortic systolic murmur conducted into neck and soft diastolic murmur at aortic area. *Fluoroscopy:* large left atrium, much enlargement of right ventricle, some enlargement of left ventricle. *Died after thoracotomy.* Severe mitral stenosis. Moderate aortic stenosis.

Group Three

C13. Male. Aged 47. S.A. 1.90 m^2. Mitral regurgitation. Disability Grade 3b. First noticed undue shortness of breath 15 months ago. Deteriorated steadily since, being now gravely disabled. No edema or hemoptysis.

Very large heart. Auricular fibrillation. Mitral systolic thrill and murmur, well conducted backwards. Mitral mid-diastolic murmur. *X-ray:* Right ventricle enlarged. Left ventricle slightly enlarged. Right atrium enlarged. Mitral valve calcified. *Operation:* rigid calcified valve with gross regurgitation.

C14. Female. Aged 36. S.A. 1.65 m^2. Mitral stenosis. Disability Grade 3b. Slight shortness of breath on exertion 17 years ago, becoming slowly but progressively worse. Now very handicapped. Ankle edema during last year. Hemoptyses last few months.

Heart only slightly enlarged. Auricular fibrillation. Moderate mitral systolic and loud mid-diastolic mitral murmurs. *Operation:* large left atrium. Moderately severe mitral stenosis with some regurgitation.

C15. Female. Aged 39. S.A. 1.65 m^2. Mitral stenosis. Disability Grade 4. Fit till three years ago when febrile illness with joint pains heralded onset of exertional dyspnoea and ankle edema. Has deteriorated steadily since. Attacks of nocturnal dyspnoea for one year. Hemoptysis once only.

Heart only slightly enlarged. Auricular fibrillation. Loud mitral mid-diastolic murmur. *Fluoroscopy:* left atrium and both ventricles enlarged. *Operation:* severe mitral stenosis, no regurgitation.

C16. Male. Aged 34. S.A. 1.76 m^2. Mitral and aortic stenosis. Disability Grade 4. Dyspnoea on exertion commenced five years ago. Deteriorated rapidly next two years and for last three years has had recurrent congestive cardiac failure. No hemoptysis. No edema at time of study.

Enormous heart. Auricular fibrillation. Clear signs of mitral stenosis, aortic stenosis and slight regurgitation, and intermittent functional tricuspid regurgitation. Systolic murmur at apex, difficult to dissociate from aortic murmur, but some conduction into axilla. *Fluoroscopy:* all chambers of heart enlarged. *Operation:* severe mitral stenosis found; no regurgitation.

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